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Study design

# Efficacy and safety of over-the-scope clips® compared to through-the-scope clips for initial bleeding control in non-variceal upper gastrointestinal bleeding: a multicenter randomized clinical trial

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## ABSTRACT:

**Introduction:** Non-variceal upper gastrointestinal bleeding still poses a serious health problem due to high rebleeding rates, despite multiple treatment options. The relatively new over-the-scope clips® technique may be an effective alternative used in clinical practice and showed promising efficacy in predominantly observational studies. However, superiority over another mechanical technique as first-line therapy has not been established yet regarding initial hemostasis and recurring bleeding.

**Methods:** The study will be a phase II, randomized, controlled, blinded, multicenter, parallel-group, superiority trial with a 1:1 allocation ratio. Adult patients with Ia-IIb Forrest classified ulcers will be randomized to either over-the-scope clips ® or through-the-scope clips. The primary outcome will be successful initial hemostasis and will be assessed by the endoscopist immediately after the procedure. Secondary outcomes will be rebleeding rate assessed by second-look endoscopy in case of substantial bleeding indicators, number of clips used, and mortality rate within 30 days. Further, the occurrence of adverse device effects will be assessed. Patient follow-up will occur periodically for a 3-month time frame.

**Discussion:** By comparing two mechanical techniques for the treatment of common ulcers, our study will provide valuable grounds to deduce recommendations for first-line definite treatment and prevention of recurrent bleeding episodes.

**Trial registration**: The trial will be registered at ClinicalTrials.gov (https://clinicaltrials.gov/).

**Keywords:** upper gastrointestinal bleeding, hemostasis, bleeding control, OTSC, clinical trial

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**Abbreviations:**

NVUGIB: non-variceal upper gastrointestinal bleeding

OTSC: over-the-scope clips

TTSC: through-the-scope clips

ASA: American Society of Anesthesiologists

ASGE: American Society for Gastrointestinal Endoscopy

ICU: Intensive care unit

HDU: High dependency unit

UADE: Unanticipated adverse device effects

DSMC: Data and safety monitoring committee

ITT: Intention-to-treat

## Introduction

Upper gastrointestinal bleeding (UGIB) is a highly prevalent medical emergency, with an annual incidence of up to 80-150/100.000 individuals (Antunes & Copelin II., 2020); it is associated with high recurrence and mortality rates (Mujtaba et al., 2020), regardless of different treatment options. Due to the high prevalence of H pylori infection and chronic NSAID use, peptic ulcer remains the most common etiology of non-variceal UGIBs, regardless of the use of H pylori eradication therapies and proton pump inhibitors. It remains responsible for 80%–90% of all UGIB (Alzoubaidi et al., 2019; Antunes & Copelin II., 2020). Overall, the rebleeding rate of non-variceal UGIB (NVUGIB) is 14.1%, and the mortality rate is around 5.4% (Barkun et al., 2004). Endoscopic evaluation is paramount in this setting for diagnostic and therapeutic purposes. The Forrest Classification (**Table 1**), which is based on specific signs of active or recent bleeding, guides the therapeutic decision-making process and assessment of the risk of rebleeding (Forrest et al., 1974). Ulcers classified as Forrest Ia, Ib, IIa, and IIb are associated with a risk of rebleeding, ranging from 40 to more than 90%, and are considered "high-risk ulcers" for which endoscopic therapy is indicated (Biecker et al., 2015; Hwang et al., 2012).

| Forrest Classification | Signs/stigma of recent bleeding |
|---|---|
| Ia | Arterial or spurting hemorrhage |
| Ib | Oozing hemorrhage |
| IIa | Visible vessel |
| IIb | Adherent clot |
| IIc | Dark base/haematin-covered lesion |
| III | Lesions without active bleeding |

**Table 1.** Forrest Classification. Adapted from "Endoscopy in gastrointestinal bleeding.", by J.A. Forrest, N. D. Finlayson, & D. J. Shearman, 1974, Lancet, 2(7877).

Several effective endoscopic hemostatic techniques are available in this clinical setting; including sclerosing agents (e.g., adrenaline, absolute alcohol, ethanolamine), thermal ablation, tissue adhesives (thrombin/fibrin glue), and hemoclips (Laine et al., 2009). Although non-inferior to each other, these therapies have been assessed in meta-analyses, where it has been demonstrated that the combination of adrenaline and a "mechanical" technique (thermal, hemoclip, or glue) reduced the rates of rebleeding, need for surgery, and death (Laine et al., 2009; Vergara et al., 2014). Therefore, this combined approach has been proposed as the standard of care by the American Society for Gastrointestinal Endoscopy - ASGE (Hwang et al., 2012). Retrospective studies have shown the superiority of mechanical therapies compared to injections or thermal modalities alone in achieving hemostasis (Naseer et al., 2020). Among mechanical therapies, hemoclips are becoming the first-line option for NVUGIB as they represent a potentially definite method. Two delivery systems are available: through-the-scope clips (TTSC) and over-the-scope clips (OTSC®). In the former, clips are delivered to the site of an implant through the endoscope's working channel; in the latter, clips are pre-mounted with a detachable cap at the distal end of the endoscope. While TTSC may be considered the current standard of care for hemoclips in the management of NVUGIB (Barkun et al., 2019), OTSC® emerge as an interesting

option for their capacity to effectively anchor into larger amounts of tissue and provide higher compression force than the predecessor (Schmidt et al., 2020). This can potentially spare patients the need for operative procedures.

Literature supporting the use of OTSC® for peptic ulcers is scarce. Nevertheless, the device has been used specifically for large and fibrotic ulcers at anatomic locations where it was difficult to implant TTSC (Goenka et al., 2017). The FLETRock study retrospectively demonstrated the efficacy of OTSC® as first-line therapy for rebleeding and mortality in NVUGIB (Wedi et al., 2018). Therefore, despite emerging evidence on the safety and efficacy of OTSC® in the management of NVUGIB (Naseer et al., 2020), clinical trials evaluating this technique as first-line therapy compared to current standard-of-care are lacking (Chan & Lau, 2017). Currently, there is not enough evidence to answer the question of whether OTSC® has higher efficacy than TTSC in achieving hemostasis and reducing the rate of rebleeding.

This study aims at comparing the use of OTSC® versus TTSC for the management of NVUGIB due to high-risk ulcers in a randomized clinical trial, by measuring successful hemostasis at the end of the endoscopic procedure. We hypothesize that OTSC® will have higher rates of bleeding control than TTSC. As an exploratory analysis, we will evaluate rebleeding rate within 48 hours and 30 days, the number of clips used to achieve bleeding control, and mortality. Regarding safety issues, we will also assess the frequency of unanticipated adverse device effects (UADE).

## Materials and Methods

*Trial Design*

A phase II, randomized, controlled, blinded, multi-center, parallel-group, superiority trial with a 1:1 allocation ratio will be conducted comparing OTSC® and standard therapy - TTSC (see **Figure 1**). The rationale for a phase II study is based on the scarce literature supporting the efficacy of OTSC® as first-line therapy for NVUGIB. Most of the available evidence

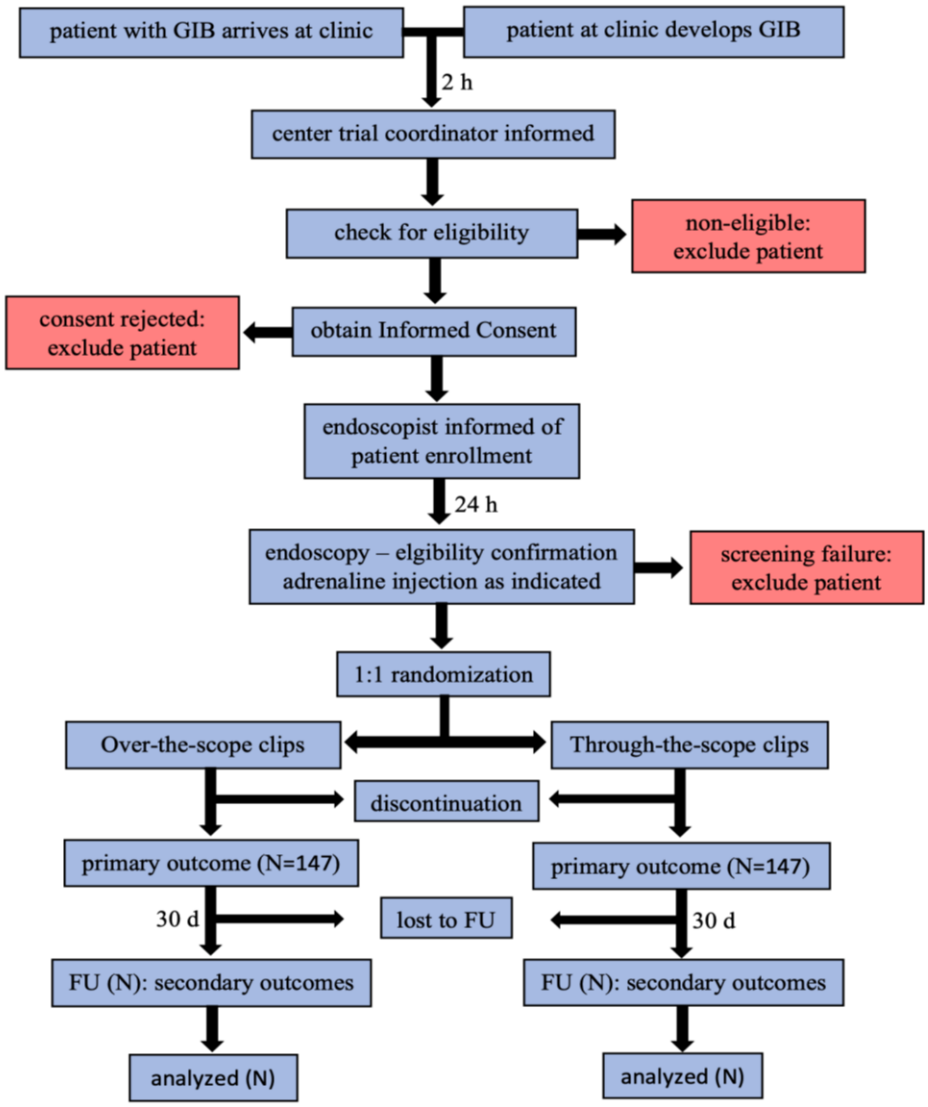


**Figure 1.** Flowchart of patient recruitment. GIB: gastrointestinal bleeding. FU: follow up. N: number of patients

comes from observational data and only a few trials. One meta-analysis examining the effectiveness of OTSC® in achieving definitive hemostasis gathered this data including 20 observational studies and one randomized controlled trial (Chandrasekar et al.; 2019). Another small trial evaluated the safety and efficacy of OTSC compared to hemostasis with hemoclips or multipolar electrocoagulation (Jensen et al.; 2020); however, in this case, only patients with Dieulafoy's lesion were assessed.

*Study Setting*

To guarantee feasible recruitment, sites must have a minimum baseline rate of endoscopic procedures in NVUGIB of at least two procedures per week. Four centers in Brazil will be included. These sites represent populations with significant geographical and cultural differences, thus increasing the generalizability of findings. Sites will be urban, tertiary centers, with appropriate conditions for treating patients with NVUGIB at each center: endoscopy, surgery, and intensive care unit, with medical specialists in these areas.

*Randomization*

After the first eligibility check, patients will be randomized in a 1:1 ratio to receive therapy - OTSC® or TTSC - using an end-to-end encrypted 24-hour operating online, central randomization service available at all participating sites. Randomization will be stratified by centers (to account for possible center variability), performed in random blocks (to secure the balance of group assignment in each center), and with variable block sizes of 4 and 6 (thus avoiding prediction of allocation). Randomization will take place immediately after full eligibility assessment during endoscopy, right before clip implantation.

Allocation will not be available in advance at any site and concealment will be ensured by the centralized system. Group allocation will only be revealed to the treating endoscopist during the procedure once all eligibility criteria are fulfilled, some of which are only to be assessed during the endoscopy. The randomization sequence will not be revealed until trial completeness - after the last included patient has undergone follow-up assessment as envisaged in the study.

*Blinding*

Patients, treating physicians, data managers, and statisticians will be blinded. Allocation will be coded using letters "A" or "B" for either group in the database to secure blinding throughout the trial. Due to the nature of the procedure, the treatment will be open label to endoscopists after a full assessment of eligibility. However, they will be unaware of the randomization method and the allocation sequence at any time during the study. An independent study nurse, with no other role in the trial, will prepare both clip types, retrieve the treatment allocation from the central randomization service (a computer next to the endoscopy room), and finally instruct the endoscopist which type of clip to use after the full eligibility assessment.

Emergency unblinding will be performed under strict consideration of life-threatening conditions. In this case, the endoscopist will unblind the treating physician and the patient. Other situations that do not represent life-threatening conditions will be assessed on a case-to-case basis and discussed with an across-site safety committee (e.g., fever of unknown origin within the first 48 hours after the procedure).

*Eligibility Criteria*

All patients will undergo hemodynamic assessment for eventual resuscitation and stabilization before further study-related treatment. Patients' eligibility will be checked before signing the informed consent and confirmed in a second step during endoscopy, immediately before the intervention.

*Inclusion Criteria*

- age: ≥ 18 years old
- suspected diagnosis of NVUGIB with the indication for endoscopy
- patient or legal representative: the ability to understand Portuguese and provide written informed consent
- high-risk peptic ulcers - Ia-IIb Forrest classification (Forrest et al., 1974; see table A.1)
- an endoscopic finding of a visible vessel > 2mm

*Exclusion Criteria*

- bleeding from a tumor or perforated ulcer that requires surgical treatment
- lesions localized in the gastric fundus or in the posterior wall of the duodenal bulb
- history of ongoing cancer therapy
- bleeding diathesis (Von Willebrand disease or hemophilia)
- pregnant or breast-feeding patients
- American Society of Anesthesiologists (ASA) classification ≥ V (Committee of Economics of the American Society of Anesthesiologists, 2020)
- patients with a history of bleeding from gastric ulcers in the last three months

*Eligibility of Centers*

Urban tertiary care centers designed according to the World Endoscopy Organization guidelines for

creating a digestive disease endoscopy unit (Mulder et al., 2013) and with a rate of at least two endoscopic procedures per week will be included. These centers are required to have full-fledged surgical units for patients to undergo complex gastrointestinal surgeries, with emergency rooms/intensive care units (ICU) and interventional radiology. Endoscopists must be qualified medical gastroenterologists with an experience in at least 130 esophagogastroduodenoscopies performed. Additionally, completion of training on OTSC® and TTSC use as required by the guidelines for privileging, credentialing, and proctoring to perform gastrointestinal endoscopy (ASGE, Hwang et al., 2012; Faulx et al., 2017) and the performance of at least ten therapeutic procedures of each are required to standardize operating experience.

*Recruitment Strategy*

The site center trial coordinator will be informed within 2 hours through physician referral of any patient admitted to the emergency room with gastrointestinal bleeding or who has developed gastrointestinal bleeding in the ICU, HDU, or ward of the center. Patients will be recruited continuously until the desired sample size is achieved. The study participants will be included after signing the written consent form which will provide complete information about the procedure's risks, benefits, and alternatives. Patients or a legal representative must be capable of a voluntary decision on whether to participate in the study while understanding the nature and bearing of the study design, interventions, and potential risks. In case any patient may turn out non-eligible for the study (screening failure), treatment will be provided as per standard guidelines and the best judgment of the treating physician.

*Adherence*

To ensure compliance, study procedures and the importance of follow-up data for the quality of research results will be explained. Regarding post-discharge visits, patients will be counseled and undergo further follow-up via the preferred method of communication (by phone call, SMS text message, WhatsApp™, or e-mail). In case of absence at a scheduled visit, patients will be contacted to reschedule the appointment. A reminder notification using the preferred method will be sent the day before the scheduled visit. If patients perceive any symptoms at any time after discharge, they are advised to come back to the center for evaluation. At such unscheduled visits, a history and physical examination, clinical laboratory tests, and endoscopy will be performed as needed. If a new endoscopy would be performed after the intervention, the findings would be classified according to the Sakita-Miwa classification for ulcer staging (active stage, healing stage, or scaring stage) (Komori, et al, 2019). Study participation may be terminated early if informed consent is withdrawn or if any serious UADE or situation occurs where the patient is unable to continue in the trial and/or the study treatment needs to be removed. This decision will be upon the physician/endoscopist in agreement with the medical monitor.

*Interventions*

Endoscopy will take place within 24 hours of the presentation of the bleeding episode once hemodynamic stabilization of the patient is achieved.

Eligible patients will be randomly assigned to OTSC® (Ovesco Endoscopy AG, Tübingen, Germany) or TTSC (Boston Scientific, Inc., USA, Resolution Clip), clips in size 12 mm. All OTSC® interventions will be performed with the 12-mm type-t clip mounted on a 6-mm cap (Ovesco Endoscopy AG, Tübingen, Germany). The injection of adrenaline (1:10.000 dilution) to improve the visibility of the lesion site is recommended - not required - in combination with clips and should be done at the endoscopist's discretion in both groups and according to the current guidelines and sites' protocols (Gralnek et al.; 2021 & Laine et al.; 2021). This will allow for the generalization of results that is focused on the clip and more patient oriented. The volume of adrenaline injection will be recorded. The number of clips used to achieve adequate bleeding control will be at the endoscopist's discretion. Assigned treatment will be discontinued upon endoscopist judgment in case continuation would harm from a medical perspective (e.g., failure of clip attachment after a few attempts). Discontinuation of clip application will be recorded as treatment failure.

*Outcomes*

Successful hemostasis during the endoscopic procedure will be the primary outcome as defined by the cessation of bleeding after the clip implant without additional endoscopic procedures and the requirement of radiological intervention or surgical treatment.

As a secondary outcome, the rate of rebleeding will be assessed. Rebleeding is defined as signs and symptoms of acute gastrointestinal bleeding manifesting as melena, hematemesis, or hematochezia and endoscopic signs of active or fresh bleeding from the treated ulcer within 48 hours (acute rebleeding) or within 30 days of follow-up (delayed rebleeding). Therefore, a second-look endoscopy will be carried out in case of possible rebleeding signs and if the following criteria apply: clinically significant bleeding (hematemesis or melena or hematochezia), a fall in

hemoglobin concentration of > 3 g/L, or shock (defined as systolic blood pressure of < 100 mmHg and/or heart rate > 100 beats/min) (Barkun et al., 2004). Other secondary outcomes will be the number of clips used and mortality within 30 days. Further, UADE will be recorded including duration, relation to the intervention, intensity, outcome, need for treatment, and seriousness.

*Data Management and Interim Analysis*

Patients will be assigned a screening ID after enrollment and subsequently a patient ID at randomization. All data will be entered electronically into a central encrypted database at each participating site. The correctness and consistency of data entry will be reviewed by a central data manager. Source data collected through paper forms will be filed at each site and stored at a lockable location, only accessible by local study staff. Participant files will be archived after the end of the study and kept in accordance with Brazilian requirements. Access to individual data will be restricted to study personnel formally authorized by the on-site principal investigator. Centers will only have access to data collected at their facility. Regular on-site monitoring visits will be installed to control the proper execution of the informed consent process, study procedures, assessments, and data entry.

UADE reports will be regularly sent to the DSMC as well as to the correspondence ethics committee and health regulatory agencies according to the local requirements. Due to the paucity of available data to support a sound estimate of the effect size to calculate the sample size, an interim analysis will be conducted at half enrollment in order to assess the efficacy and safety of OTSC® over the TTSC. The DSMC will assess the occurrence of significant safety issues (UADE) with the set p-value-criterion in the interim analyses to ensure that the potential benefits of the trial outweigh the risks. If relevant safety concerns are present or the efficacy will not be achieved, the DSMC can vote for early termination of the trial and the sponsor can do so. The Haybittle-Peto stopping boundaries (Haybittle, 1971) will be used, considering threshold values for interruption of $p < 0.001$ for safety and $p < 0.0001$ for efficacy.

*Sample Size Calculation*

STATA IC 16© software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) was used to calculate the required sample size based on the primary outcome (successful hemostasis). The effect size was calculated based on the difference between the proportion of successful hemostasis reported by different studies and an estimated minimal clinically significant difference of 10%. According to the ASGE guidelines (Hwang et al., 2012), Gevers et al. (2002) showed successful hemostasis of 85% when comparing TTSC to adrenaline as first-line therapy in patients with non-variceal upper gastrointestinal bleeding (Raju et al., 2004; Gevers et al., 2002). On the other hand, two retrospective studies demonstrated that OTSC® achieved 96.4% (Manta et al., 2018) and 92.4% (Wedi et al., 2018) of successful hemostasis when used as first-line therapy. Based on that information, we performed a sensitivity analysis using an alpha of 0.05, power of 80% and 90%, and effect size of 11.4% (difference in proportions between both treatments). A two-sided test estimated a sample size of 202 with a power of 80% and 270 with a power of 90%. Then, we decided to conduct the main analysis with a power of 80% for better feasibility. To account for the screening failures, due to the prevalence of the other types of ulcers meeting exclusion criteria, 45% were added to that value resulting in 294 participants - 147 per arm.

*Statistical Analysis*

The statistical analyses will be conducted using STATA IC 16© and based on the intention-to-treat (ITT) principle. Absolute and relative frequencies will be used to describe categorical outcomes. Continuous variables will be described by the number of observations, mean and standard deviation, or by the median and interquartile range if data distribution demands. The primary outcome - successful hemostasis - and the secondary outcomes - rebleeding rate (acute or delayed) and death within 30 days after the procedure - will be analyzed by Fisher's exact test for the categorical data level of variables. The secondary outcomes - the number of clips - will be analyzed by the Student's t-test or the Mann-Whitney-U test depending on the assessment of test assumptions as to the continuous data level of variables. Exploratory analyses will be performed on outcomes of interest using logistic regression for categorical data and multiple regression for continuous data, adjusting for the volume of adrenaline injection, age, the experience of the endoscopist (number of procedures previously performed), comorbidities (hypertension, diabetes, chronic renal insufficiency), and the use of anticoagulant/antiplatelet medication. The absolute and relative frequency of serious and non-serious UADE will be evaluated.

Given the immediate assessment of the primary outcome during the endoscopy, we do not expect missing data for the primary outcome. However, for secondary outcomes, as data is collected among hospitalized and recently discharged patients until 30 days of follow-up, we expect missing data at random and

will perform ITT analyses using multiple imputation methods. To ensure robustness, as sensitivity analysis we will assess the primary outcome - successful hemostasis - by adjusting for centers in the logistic regression and conducting a per-protocol analysis. Furthermore, due to the clinical relevance of rebleeding rates and the potential occurrence of drop-out, a worst-and-best-case scenario analysis will be performed in order to verify the results provided from the analysis by the multiple imputation method.

## Discussion

Failure of therapeutic endoscopic methods in patients presenting with NVUGIB leads to rebleeding and may require surgery as this condition is associated with high mortality. A meta-analysis showed that older hemoclips were not superior to other hemostatic endoscopic methods regarding initial hemostasis, rebleeding, surgery, and mortality rate for NVUGIB from peptic ulcers (Yuan et al., 2008). TTSC are widely used to achieve hemostasis as first-line therapy, while OTSC® is considered a suitable alternative as first-line treatment (Naseer et al., 2020) despite lacking experimental evidence. Several limitations of the one precedent clinical trial (STING) will be addressed in our study: 1) patients with first-time bleeding were excluded (as they studied OTSC for rebleeding), which we will include improving the prevention of further bleeding episodes, 2) recruitment rates were heterogeneous among the participating centers which we will address by stratified block randomization method and inclusion of high patient admission rates, 3) it was an unblinded study which we will address by blinding patients and study staff as much as possible, 4) possible carry-over effects due to crossover design may have been present which we will address by choosing a parallel-group design (Schmidt et al., 2018). Further strengths of our trial are using a similar comparator, an objective outcome, a stepwise eligibility process, and an immediate assessment of the primary outcome to prevent high drop-out rates. Even with negative results, our study will provide valid information for clinical practice due to the robust design. However, some limitations need to be considered. The final assessment of eligibility criteria will be carried out by endoscopists to whom the treatment becomes open label right after. Thus, a risk for incorrect discontinuation emerges.

Further, the endoscopist's experience may affect the main outcome. To address these issues, we will ensure that the endoscopists have a minimum amount of expertise and will be trained to be familiar with both techniques. In addition, we will also assess how the endoscopist's experience affects the primary outcome - successful hemostasis - including the number of procedures performed by the endoscopists in a logistic regression model. Moreover, the inclusion of the number of clips as a secondary outcome will provide sound data for the development of a cost-effectiveness trial. NVUGIB remains a worldwide health problem due to its high incidence and therefore the establishment of new definite first-line methods for effective acute bleeding control and prevention of further bleeding episodes is urgently needed. OTSC® seems to be a promising approach, especially for high-risk ulcers.

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